Citation:

Pimenta E, Gaddam KK, Oparil S, Aban I, Husain,Dell'Italia LJ, Calhoun DA. Effects of Dietary Sodium Reduction on Blood Pressure in Subjects With Resistant Hypertension Results From a Randomized Trial. *Hypertension*. 2009 Jul 20. [Epub ahead of print]

PubMed ID: 19620517

Study Design:

Randomized, crossover trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine the effects of dietary sodium restriction on office and 24-hour ambulatory blood pressure in patients with resistant hypertension.

Inclusion Criteria:

- Patients had resistant hypertension, defined as uncontrolled hypertension [systolic blood pressure (SBP) greater than 140 or diastolic blood pressure (DBP) greater than 90mmHg] determined at ≥ two clinic visits despite the use of ≥ three anti-hypertensive medications at pharmacologically effective doses
- Patients who had been on a stable anti-hypertensive regimen, including a thiazide-type diuretic, for at least four weeks before enrollment.

Exclusion Criteria:

- Subjects with a history of atherosclerotic disease (myocardial infarction or stroke in the previous six months), congestive heart failure or diabetes on insulin treatment
- Subjects with an office blood pressure greater than 160/100mmHg.

Description of Study Protocol:

Recruitment

Consecutive subjects recruited to the University of Alabama at Birmingham Hypertension clinic for resistant hypertension were recruited.

Design

Four-week, randomized crossover trial with two one-week interventions (low- or high-salt diet) and a two-week washout period.

Dietary Intake/Dietary Assessment Methodology

Compliance with dietary regimen was assessed by 24-hour sodium excretion, not dietary record.

Blinding Used

Not blinded.

Intervention

- Subjects completed two one-week interventions (low- or high-salt diet) and a two-week washout period (regular diet)
- Low-salt diet: All low-salt meals and snacks were provided and formulated to contain 50mmol of sodium per day Two diets with either 2,000 calories (31.2% fat, 48.4% carbohydrate and 20.4% protein) or 2,500 calories (30.8% fat, 50.4% carbohydrate, 18.8% protein) were provided to maintain subjects' baseline body weight
- High-salt diet: 6g per day of sodium chloride was added to subjects' regular diet to increase dietary sodium to greater than 250 mmol per day.

Statistical Analysis

- Mixed modeling for repeated measures was used, the effect of treatment order was assessed and changes in 24-hour ambulatory blood pressure monitoring were calculated
- The sign test was used to test mean differences assuming that time order was not significant and exact binomial confidence intervals for the median were reported.

Data Collection Summary:

Timing of Measurements

Body weight, office blood pressure, and 24-hour ambulatory blood pressure monitoring, biochemical evaluation, pulse wave analysis and pulse wave velocity were determined immediately before randomization and at the end of each one-week dietary intervention.

Dependent Variables

- Aortic pulse wave velocity: A marker of arterial stiffness, calculated from measurements of common carotid and femoral artery wave-forms using an automatic applanation tonometry-based device
- Aortic augmentation index: A marker of arterial stiffness, quantified as a percentage of aortic pulse pressure
- Office systolic and diastolic blood pressure: Seated, after five minutes of rest
- 24-hour ambulatory blood pressure monitoring: Recorded blood pressure every 20 minutes during the day and every 30 minutes during the night
- Biochemical analyses: Serum potassium, creatinine, brain natriuretic peptide, plasma aldosterone and plasma renin activity
- 24-hour urine collections: Aldosterone, sodium, potassium and creatinine
- Body weight.

Independent Variables

Low- or high-salt diet.

Control Variables

Treatment order.

Description of Actual Data Sample:

- *Initial N:* 13
- *Attrition (final N):* 12 (four males and eight females)
- *Mean age:* Standard deviation of 55.5 (9.4) years
- *Ethnicity:* Six black, six white
- *Other relevant demographics:* None
- *Anthropometrics:* Mean (standard deviation) body mass index of 32.9 (6.3)kg/m^2
- *Location:* Alabama, US.

Summary of Results:

Key Findings

- Mean office systolic and diastolic blood pressure were reduced by 22.7mmHg (95% CI, 11.8-33.5mmHg) and 9.1mmHg (95% CI, 3.1-15.1mmHg), respectively, during low- compared to high-salt diets
- Low-salt diet decreased office, daytime, nighttime and 24-hour systolic and diastolic blood pressure significantly compared to high salt ingestion.

Variables	Mean Change Between High- and Low-salt Diet, 95% Confidence Interval	Statistical Significance of Group Difference (P-value)
Augmentation index, percentage		0.0554
Pulse wave velocity, m/s		0.1671
Office blood pressure, systolic, mmHg	-22.7 (-33.5, -11.8)	0.0008
Office blood pressure, diastolic, mmHg	-9.1 (-15.1, -3.1)	0.0065
Ambulatory blood pressure monitoring, mmHg (24-hour systolic)	-20.1 (-28.1, -12.1)	0.0002
Ambulatory blood pressure monitoring, mmHg (24-hour diastolic)	-9.8 (-13.8, -5.8)	0.0002

*P-value and 95% confidence interval are based on the sign test.

Other Findings

- Pulse wave velocity and aortic augmentation index decreased with low compared to high-salt diet, but not significantly (P>0.05)
- The reductions in brain natriuretic peptide, body weight and creatinine clearance and the increase in plasma renin activity are indicative of a reductionin intravascular volume
- After statistically correcting for testing multiple variables, only office systolic blood pressure and all ambulatory blood_pressure monitoring remained significant.

Author Conclusion:

Dietary salt restriction substantially reduced both office and 24-hour ambulatory blood pressure, demonstrating that excessive salt ingestion contributes importantly to elevated blood pressure levels in patients with resistant hypertension.

Reviewer Comments:

Strengths

Crossover, randomized design, use of 24-hour ambulatory blood pressure monitoring and confirmation of dietary adherence with 24-hour urinary sodium excretion measurements.

Limitations

Evaluation of a relatively small number of subjects, unblinded administration of the salt diets and short duration of the dietary treatment periods.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes

4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	No
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	No
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A

7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	???
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	No
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes